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<<Stephen Scala, Analyst, Cowen and Company, LLC.>>

Good morning, and welcome to the GSK session of the Cowen conference. We're very, very pleased to have GlaxoSmithKline back with us this year. Representing the Company is Axel Hoos, who is Senior Vice President of Oncology R&D. Axel is a true pioneer in immunology, having been involved in the development of some key assets, which were the pioneers of the IO opportunity, which now we size at $30 billion in 2022. And to explain how GSK will participate in that massive opportunity, there's no better person than Axel. So, I'll turn it to you.

<<Axel Hoos, Senior Vice President, Oncology R&D>>

Good morning. Thank you for having me. So, what I'd like to do is reintroduce you to GSK oncology. As you are aware, about two years ago, we had a transaction with Novartis that divested our marketed oncology products to Novartis. That marketed oncology portfolio was mostly comprised of targeted therapies and, in some instances, novel mechanisms, like the BRAF and MEK inhibitors, in some instances, me-too products, like HER2 or CD20 targeting agents.

So, what that did for us was it gave us a cash injection, and it enabled us to have a clean slate for an entirely innovative and more focused new oncology portfolio. So, what I'm presenting you now is a snapshot of that new R&D portfolio that has been focused on three areas of science, as you can see here, cancer epigenetics, where we have a history since 2008 and have built a deep pipeline, likely the most in-depth pipeline for epigenetic agents in the industry.

For immuno-oncology, we have about a five-year history and focused on a diversified next-generation pipeline of assets that can lead to transformational combination therapies and then the cell and gene therapy presence, which we spun out of immuno-oncology, and that has been formalized as a separate unit just last year. It's built on partnerships and a platform in house. That platform actually has, since it started with the rare disease space, delivered the first marketed cell and gene therapy product in the industry with Strimvelis that was approved last year.

So, and from that rare disease position, we're now moving into oncology to scale and make the platform workable for larger indications in the cancer space. So, overall, our intent here is to focus entirely on innovation and maximize patient survival through either monotherapy or

combinations emerging from this new pipeline. A few main trends that we see in the industry that we're participating in, first, begins with standard of care replacement. We have seen now since the advent of immuno-oncology that standard of care, particularly older chemotherapies, are completely disappearing. We're seeing this happen in increments. But, it comes with a substantial improvement in patient survival, which is fully aligned with the strategy I've just outlined.

Now, we're beginning to also understand the immune profiles of patients, which enables us to give the right therapy to the right patients. This is complex. So, there's a lot of work to be done, a lot of collaborations to be forged to fully understand, where do we put new medicine to treat the right patients? Complex combinations are at the forefront. There is at least 1,000 combination therapy trials going on across the industry at the moment. And we are looking towards understanding the biology better and improve our endpoints. So, using standard oncology endpoints, of course, we'll continue, but there are new endpoints to be considered that particularly capture the biology of immuno-oncology agents.

And then at last, we are beginning to build new toolboxes of completely different modalities. And I think cell and gene therapy is a good example for that that enables us to achieve transformation effect. That toolbox is bigger and more diverse than it has ever been. And it forces us to really think carefully about collaboration and how do we combine assets to achieve transformation effects? Now, here's a snapshot of the oncology pipeline at GSK at present in the three areas of science, as I had outlined. This pipeline has now 11 assets in the clinic. And I'm not focusing on the discovery portion of it. There's a much larger discovery portion, which will allow for pipeline sustainability.

I will just give you a few highlights of what we have. So, right now, in the immune checkpoint modulator space, the next-generation checkpoint modulators are focusing on agonist antibodies instead of antagonists as the PD-1s and CTLA4s have been so far. OX-40 and ICOS are two targets that we believe are important, ICOS in particular, and I will come to that again in a minute. They are in the clinic since last year and are beginning to deliver first data that enable us to say where we can use them best. Then we have a BCMA antibody drug conjugate, which is an immunogenic cell death inducer that has just shown proof-of-concept.

The first data was shown at ASH last year. I will come to that again in a minute. A TLR4 agonist that has just entered the clinic earlier this year, which we view as a good combination agent to create those transformational combinations from within our own pipeline. And then several other immuno-oncology programs in three different areas, small molecule targets to modulate the tumor microenvironment. ImmTacs, which is a partnership with Immunocore, this is a bispecific antiformat that uses an affinity matured T-cell receptor in an antibody construct. The first program will likely go into the clinic in the beginning of 2018.

And then we have several bispecific antibody platform efforts, which I view as the next generation of innovation in this area, a mAb-dAb platform which exists within GSK, and then a dual-specific antibody platform, which is a partnered effort with Adimab. If we switch from immuno-oncology to epigenetics, there are four epigenetic compounds in the clinic, as they're named here, a BET inhibitor, an LSD-1 inhibitor, an EZH2 inhibitor, and a PRMT5 inhibitor, all novel targets addressing different epigenetic mechanisms.

Then we have a PI3K-beta inhibitor, which is in the clinic, and several novel small molecule approaches to target other epigenetic targets that are unique and give us the largest pipeline in this area. And then finally, in the cell and gene therapy space, there's one asset in the clinic, a partnered molecule with Adaptimmune, which has shown up to 50% response rate in a soft tissue sarcoma indication. So, it shows that you can carry cell and gene therapy efforts into solid tumors as compared to most of the data that exists on CAR-Ts and hematologic malignancies.

So, we're making some progress towards entering the much larger solid tumor space. And again, here, we have several discovery programs around CAR-Ts and TCR-Ts in the preclinical space. And then finally, there is a Notch2/3 blocking antibody that is a partner program with OncoMed. I call that a legacy program because it doesn't fit any of the other three categories. It will read out data in the first half of this year from a randomized Phase 2 trial in small cell lung cancer. And we will then be able to make an option decision on this compound.

Now, let's look at the strategy a little bit more carefully. When GSK began its immuno-oncology efforts about five years ago, that was after ipilimumab approval when the PD-1 wave began, we had to make a decision since we had no compounds at that time. We wanted to enter the space. We knew the space was really just launching. So, there's a lot of room to maneuver. So, we chose to prepare ourselves for the next generation. Instead of trying to compete on PD-1, we decided we go to the next generation. And five years in, we're now among the contenders for a leadership position for the next generation.

So, a quick overview of what do we actually have in this next generation of immuno-oncology. When you break down the immune system into the three major components, which are in the adaptive immunity area T-cell activity; B-cell activity, so making antibodies against disease; and then innate immunity, the more unspecific type of immune response that includes NK cells, macrophages, and so on; then you can see underneath those three blue boxes multiple modalities that you can use to actually target those immune mechanisms. The green boxes represent approved therapies in those categories. And the white space leaves a lot of opportunity for us to actually make more progress and offer new mechanisms, target new mechanisms with immuno-oncology agents. So, there's a huge opportunity here and a lot of blank space.

Now, GSK, now coloring this in the GSK orange, has decided to create a diversified pipeline that enables us to combine assets from within the pipeline for transformational effect. So, we have a either clinical or discovery program in either of those orange colored boxes, which shows it's a diversified approach, and they will play together nicely. I will show you data on that in a moment. Now, here's the first example. The first proof-of-concept from the new pipeline in a first-in-human trial in multiple myeloma refractory disease post standard of care has shown a 67% response rate with a BCMA antibody drug conjugate.

So, BCMA is a B-cell maturation antigen, a highly expressed target on multiple myeloma cells and some patients with non-Hodgkin's lymphoma. In this area, we have seen 30% response rate with previous agents. Nobody has had an agent that has that high of a response rate as a monotherapy that early in development. And we have now filed for breakthrough designation. We will see how this unfolds. But, we believe that this has a high probability of becoming a medicine that will contribute to the treatment of multiple myeloma.

For OX-40, we're not the only company that has an OX-40 antibody in the clinic. There are at least five that I'm aware of. OX-40 offers a dual mechanism. It can enhance T-cells against disease, so effector cells, and it can also suppress regulatory T-cells, so taking a bit away of the breaking mechanism of the immune system. So, OX-40 is a complex mechanism of action. Despite multiple clinical programs running, we have not yet cracked the code how to best use OX-40. But, this is the opportunity to actually identify the right patient population through biomarker work to give the right agent to the right patient.

So, OX-40 combines very well with other assets. I'm showing you here preclinical data as our clinical data is not yet ready. OX-40 and PD-1 combines very well, as the upper graph in the right upper corner. And TLR4, our own agent, combines very well as well. So, we have a partnership with Merck to combine OX-40 with KEYTRUDA. That combination dose escalation is currently ongoing. And we expect to have TLR4 in this combination in the clinic in the second half of this year.

Now, switching to ICOS, ICOS is a less competitive target. Here, we have put the first agonist antibody in the clinic last year. And it is a highly engineered antibody that avoids cell depletion and focuses strictly on the agonist function of the antibody, which is how this target was actually identified as a therapeutic target. It originates from the ipilimumab program as a biomarker, where we have found that patients that overexpress ICOS or induced ICOS expression post ipilimumab therapy are those patients that induce responses and are patients with a longer survival.

So, it seems that the ICOS overexpressing T-cells are the carriers of that clinical benefit. So, enhancing those T-cells, pushing them to proliferate and increase the size of the army that can

fight the disease is what this ICOS agonist antibody is intending to do. And on the right side here, you can see the data from the ipilimumab program showing the correlation of response and survival with the target. And then on the right, the agonism of that target in human T-cells shows T-cell activation and proliferation is being induced. And we're testing this now in a first-in-human trial. And the PD-1 combination is poised to start in the second quarter of this year.

Now, TLR4 agonist has just entered the clinic in a first-in-human trial in healthy volunteers to determine a dose and a safety profile. And once we have that, we will move it into a combination with OX-40 and other assets in our pipeline. That's expected to be later this year. TLR4 is an interesting mechanism. It's different than just activating T-cells through checkpoints. It activates dendritic cells for antigen presentation. And it enhances innate immunity and modulates the tumor microenvironment for T-cells to be more effective in the tumor. So, that combination with a T-cell activating agent like OX-40 seems to be very promising.

On the right side here, you can see preclinical data where TLR4 and OX-40 as well as TLR4 and ICOS are highly synergistic. Now, in the cell and gene therapy space, as I have said, we have a partner program with Adaptimmune that is an affinity matured T-cell receptor against the specific target, in this case NY-ESO-1 that exists on several solid tumors, particularly strongly expressed on synovial sarcoma. So, the data I'm showing you here is from this first-in-human study in synovial sarcoma. It's about 50% response rate, which is fairly high. No other therapy in this disease has ever achieved that.

And we're now looking towards assuring that this is durable and that we can carry it into other diseases. So, we're testing this in multiple myeloma. And there are trials in ovarian cancer and non-small cell lung cancer ongoing. The therapy has obtained breakthrough designation from the FDA and prime designation from the EMA. And we are moving this program forward as quickly as we can towards a pivotal study and towards further exploration and further engineering to enhance the activity and enhance the durability of this compound.

Now, one important thing I'd like to say around the way GSK conducts its work in oncology, we're heavily partnering with other organizations, be that academic centers or be that pharmaceutical companies, in order to achieve the best science and in order to move our compounds more quickly through the clinical – initial clinical trials and then into combinations. So, on the left here, you can see which cell therapy partnerships we have between Adaptimmune for the TCR-Ts; and Miltenyi Biotec for supply chain optimization and automation as well as optimizing CAR-T cells; University of Pennsylvania, which is one of the pioneering academic organizations in cell therapy; Tiget, which was the organization in Italy that has done the ADA-SCID work with us and led to the marketed product Strimvelis that I mentioned earlier; MolMed for manufacturing; and then several others that are not yet publicly disclosed.

So, what that ultimately comes down to is we're looking at cell and gene therapy as a platform effort with a long-term view to make cells into medicine, so create another modality beyond antibodies in the biologic space that can help us make new medicines on a regular basis. So, we begin with something complex, like TCR-Ts, but we will carry this into other settings as our platform allows us to do that. Now, on the right here, you see the academic centers, which are the best cancer centers in the world, that we have partnered with to do our translational research efforts for the clinical programs that I just presented.

Now, let's say a few words about the epigenetics part of the pipeline. As I mentioned, this is a large effort here in epigenetics. We have more than 20 programs in total. Of these, four are in the clinic. When you look at how epigenetics works as compared to regular genetics, targeted therapies have – look for mutations in tumors, identify those mutations, targeted them with a small molecule or an antibody approach, and then has moved those into a new medicine space. Now, what we have here is the layer of the information above the gene. So, we're not looking at genetic mutations in tumor-suppressive genes or oncogenes. We're looking at mutations in the reading, writing, or erasing mechanisms or for the transcription of those genes, which makes a big difference and enables us to enter a whole universe of new targets that contribute significantly to cancer development.

So, we have four programs in the clinic here, one in – at least one in each category of epigenetic mechanisms. So, I'll give you one example. The BET inhibitor is the furthest along in the clinic. It is quite versatile and has activity preclinically in a variety of tumor types. What you can see here is inhibitory activity against a variety of cancer types. Each color on that diagram represents a different cancer type where we can inhibit cell growth very effectively. Now, if we take that into the clinic, we presented data on our first indication, which is a small indication driven by a BET mutation in NUT midline carcinoma at AACR last year. The data indicated about a 22% response rate in – at the dose at which we believe we can achieve clinical effect and that we can carry forward in clinical development.

Now, progress we have made since AACR last year ranges mostly in expansion cohort data generation in prostate cancer, breast cancer, small cell lung cancer, and some more data in NUT midline carcinoma, which likely will be our first indication to achieve a proof of concept in. Then we're also focusing on combination therapy, as preclinically, these agents combine very well with standard of care mechanisms. So, in breast cancer, we are combining with fulvestrant. In prostate cancer, we are combining with abiraterone or enzalutamide. And there are several other combinations in preparation.

So, overall, BET is a versatile molecule that has shown clinical activity and that we are pushing on multiple fronts to find the best place for it to become a medicine. Now, if I summarize this in total, GSK oncology has now reemerged with an innovative new portfolio that aims to maximize

patient survival and aims to have sustainability for us to grow back into a leadership position in this space. So, we have skipped the second generation of immuno- oncology compounds and are now among the leading companies that have new mechanisms for the third generation. And as you know, the jury is out for the third generation. There are no success stories in that area yet, but a lot of promise.

So, now, we have a diversified pipeline. We focus on innovation. We are building a world-class team now in discovery and in development. So, this is a seamless process at GSK. As compared to many other partners in the industry, we don't separate discovery and development. We do make that a seamless process and therefore have a much faster drive of an asset through the system.

And then finally, we focus on partnership to achieve the best science and access to combination therapy, like our partnership with Merck on KEYTRUDA. So, with that, we think pipeline sustainability will be available once we have the first assets that are actually going back to the market. And our pipeline is set up that, every year, several new molecules can enter the clinic and can be further investigated.

So, with that, I think I'm at the end of this overview, and I'm happy to take some questions. Please.

Q&A

<Q>: [Question Inaudible]

<A – Axel Hoos>: Yes, so CTLA4 has become a molecule that got back into the spotlight. It was what initiated immuno-oncology, as we all know. And it is a central mechanism in T-cell activation. So, clearly, it's an important target. I don't think it's going away. But, we follow the same strategy here as we follow for PD-1. So, we decided not to duplicate what others that are far ahead of us on some of the early mechanisms of immuno- oncology are already doing. So, for CTLA4, we will partner with a leader instead of trying to catch up. We're doing the same thing with PD-1, and then we will focus on new mechanisms that will enable us to have our own position in the space.

And the one thing I can say is, even though there's a lot of activity here and, as I said, there's a lot of money spent on PD-1 or CTLA4 antibody investigation, there is no shortage of opportunity to leverage other mechanisms to fill the blank spots in the clinical benefit picture for patients. We haven't cured everybody yet. There's a lot more to be delivered. And CTLA4 is probably a good combination agent. And we will do work for CTLA4, but not through our own molecules. It will be done in partnership.

<Q>: [Question Inaudible]

<A – Axel Hoos>: Yes, so we have not yet found out how OX-40 can be best clinically developed. So, you might know, from the early phase data that has been shown by the companies that have presented data on OX-40, there are no major response rates yet. And we have not even determined the right dose for those antibodies. So, if I give you a quick differentiator between the antagonist antibodies and the agonist antibodies, the antagonists, they – you can dose them up to a certain level. Then at that point, maximum inhibition is achieved, and dosing more will not make a difference. And we have seen that clinically in several settings.

For agonist antibodies, you might actually overstimulate the cell, exhaust the cell, and then potentially lose the effect. So, there is a narrow therapeutic window that needs to be found. And we need to find the right patient population because all these agents interact with each other. The immune system is a complex organ. So, if you give a PD-1 blocker, you upregulate OX-40. Then all of a sudden, the OX-40 environment for giving OX-40 agonist antibody has changed. And if you give it in combination with PD-1, it needs to be titrated properly in the right context. And it is too early for us to say what the right situation is in which to best use these assets. We do know, mechanistically, it's a potent mechanism and a relevant mechanism in the immune system. So, we should be able to leverage it therapeutically. But, there is no company yet that has actually found the right way to do it yet. So, in terms of differentiation, to your question, we will differentiate if we find the mechanism. And whoever gets there first will likely lead in the OX-40 space.

<Q>: [Question Inaudible]

<A – Axel Hoos>: Yes, we had expected there could be more toxicity. We certainly prepared ourselves for that. And the dose escalation of these early human trials has been very cautious. Now, we're working with the data. So, I cannot explain the mechanisms in terms of the toxicity observations. It has been more focused and more mild than we had expected. But, as it has been in the CTLA4 space, with increasing dose and then with increasing hitting the right mechanism, you actually start seeing toxicity. So, we're not yet in a place where we can say we won't have toxicity, once we find the right patient setting in which these agents work best.

So, I wouldn't relax about this yet. It's not 100% clear yet. Another question.

<Q>: [Question Inaudible]

<A – Axel Hoos>: Yes, so the BET inhibitor behaves in many ways like a targeted therapy or in some ways also like a chemotherapy. So, we see conventional toxicities, like thrombocytopenia,

neutropenia, and in some instances fever and fatigue, classic symptoms that you have with other agents. They can be clinically managed. And they have been managed very well by the physicians that are conducting the studies. And as we treat more patients and especially in combination, we will be able to consolidate the safety profile further. But, your point is well taken. This is a more conventional safety profile as compared to what we have seen with immuno-oncology agents.

<Q>: [Question Inaudible]

<<Axel Hoos, Senior Vice President, Oncology R&D>>

Thank you.